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Successful prevention of transmission of integrase resistance in the Swiss HIV Cohort Study

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Abstract

Prevalence of integrase inhibitor (INSTI) transmitted drug resistance (TDR) may increase with the increasing use of INSTIs. We analysed the prevalence of INSTI TDR in the Swiss HIV Cohort Study (2008-2014). In 1 of 1,316 (0.1%) drug-naïve samples a major INSTI TDR mutation was detected. Prevalence was stable although INSTIs were increasingly used. We showed that this is in contrast to the introduction of previous drug classes where more treatment failures with resistant strains occurred and TDR was observed more rapidly. We demonstrated on a population-level that it is possible to avoid TDR affecting a new drug class for years.

Introduction

Integrase strand transfer inhibitors (INSTIs) are increasingly prescribed to treat HIV-infected patients [1]. As INSTI-use and subsequent treatment failures increase, the number of transmitted INSTIs resistance is expected to increase in analogy to other drug classes [2, 3]. The risk of transmission of drug resistance is particularly high in populations where treatment-experienced patients are not on suppressive antiretroviral treatment (ART) [2].

Despite increasing use of INSTIs, transmission of INSTI resistance has not been widely reported [4, 5]. There are some anecdotal cases where the transmission of major INSTI drug resistance was reported [6, 7]. Minor resistance mutations are most likely polymorphic and occur more often in non-B subtype compared to subtype B infections [4, 5].

We aimed to analyze the prevalence of transmitted INSTI resistance in the Swiss HIV Cohort Study (SHCS) and to identify risk factors for its occurrence. In addition, we intended to specify the transmission potential for INSTI drug resistance in the SHCS population and to set it in historical context.

Methods

Study population

We used data from the SHCS and the SHCS drug resistance database. The SHCS is an ongoing, nationwide, multicenter, clinic-based observational study [8]. The SHCS is highly representative and includes 85% of the newly infected patients and at least 75% of patients on antiretroviral treatment in Switzerland [2, 8]. Sequences from genotypic drug resistance tests (GRTs) are stored in a central database (SmartGene; Integrated Database Network System IDNS® version 3.6.14) [2]. Subtypes were defined using REGA HIV-1 Subtyping (V3.0)

(http://dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool#). If results returned inconclusive, the analysis was repeated with Comet subtyping (V1.0) (http://comet.retrovirology.lu/). The SHCS has been approved by the ethical committees of all participating institutions, and written informed consent has been obtained from all participants [8].

The SHCS drug resistance database contained 1,724 GRTs from the HIV-1 integrase gene, 1,168 were prospectively and 556 retrospectively sequenced. 1,521 of 1,724 GRTs were from INSTI-naïve patients and 1,057 of 1,724 from treatment-naïve patients. The retrospective sequencing was done systematically. All available samples from patients who were in the time period 2008-2011 newly diagnosed with HIV were sequenced as well as baseline samples of drug experienced patients who started INSTI-containing treatment and patients who failed on INSTIs.

INSTI drug resistance

To estimate the prevalence of transmitted INSTI resistance up to the year 2014, we included 1,316 patients who had ≥1 GRT performed from the integrase gene before the first exposure to an INSTI (earliest GRT per patient chosen). Samples retrieved before 2008 were summarized in a group: ≤2008. We considered drug resistance mutations listed by IAS-USA 2015 and differentiated between minor (T66AK, L74M, E92G, T97A, E138AK, G140AS, R263K) and major mutations (T66I, E92Q, F121Y, Y143CHR, S147G, Q148HKR, N155H) [9].

We performed a logistic regression adjusted for HIV subtype to quantify the impact of calendar year on transmitted INSTI resistance.

To account for potential reversion of transmitted drug resistance mutations in the absence of drug pressure, we performed a sub-analysis including only GRTs from recently infected, treatment-naïve patients. A recent infection was defined as follows (details are described elsewhere [2]): acute HIV-1 infection described by the physician, or documented seroconversion (<1 year between the last negative and first positive test), or an ambiguity score ≤0.5% combined with a CD4 cell count >200 cells/µL [10].

Transmission potential of drug resistance

To estimate the transmission potential of INSTI drug resistance and to put our findings into a historical context, we compared different aspects of the time period after the introduction of INSTI (2008-2014) to the time periods after introduction of NNRTIs (1998-2004), unboosted PIs (1996-2002) and ritonavir-boosted PIs (PI/r) (1999-2005). We differentiated unboosted PIs and PI/r because of the better potency of PIs/r. We compared the number of patients on the specific drug classes, the number of failures and the number of patients detected with ≥1 drug resistance mutation affecting the specific drug class. Additionally, we compared three different types of population viral load (PVL): 1) PVL after first exposure to the specific drug class (after ≥120 days of continuous treatment), 2) PVL after treatment failure on a specific drug class, and 3) PVL after detection of the first major drug resistance mutation affecting the specific drug. To calculate the PVL, we summed the log10-transformed viral loads from the respective patients. Each patient contributed to each year once. If a patient had ≥2 measurements within the same year, we calculated the mean of the log10-transformed viral load.

Treatment failure was defined as ≥1 viral load ≥500 HIV-1 RNA copies/mL (after 180 days of continuous treatment or previous viral suppression) followed by a treatment change or stop. Statistical analyses were performed with Stata SE Version 14.0 (StataCorp, College Station, TX).

Results

Transmission of INSTI resistance mutations

INSTI resistance mutations were rarely detected among INSTI-naïve patients (Appendix 1). Only one major mutation was found (1 of 1,316, 0.1%). It was T66I, found in a sample retrieved in 2001. In 38 of 1,316 (2.9%) samples viruses were found with minor INSTI resistance mutations. The most common minor mutations were L74M (17 of 1,316; 1.3%) and T97A (16 of 1,316; 1.2%). Minor

mutations were more common in subtype non-B compared to subtype B infections (24 of 466; 5.2% vs. 14 of 850; 1.6%; Fisher's exact p-value <0.001). The detected minor mutations were most likely polymorphic. They were already present before (in 4 of 157 samples; 2.6%) the introduction of INSTIs in Switzerland (28 February 2008). We found no evidence for an increase in prevalence of minor mutations in the years after the introduction of INSTIs. The yearly prevalence was 2.4% (95% CI: 0.6-5.9), 3.8% (1.4-8.2), 2.4% (0.8-5.4), 3.6% (1.8-6.6), 2.5% (0.8-5.8), 1.3% (0.2-4.7) and 3.9% (1.5-8.4) in 2008 to 2014. The odds ratio (OR) per calendar year was 0.98 (95% CI: 0.8-1.2) when performing a logistic regression adjusted for HIV subtype B vs. non-B (OR: 3.3, 95% CI: 1.7-6.4, p=0.001).

The results were similar when we restricted the analysis to recently infected patients. No major mutation was detected in 303 samples. Minor mutations tended to be more common in subtype non-B (4 of 92 samples, 4.4%) compared to subtype B infections (3 of 211 samples, 1.4%, p- =0.205).

Potential reasons for the low prevalence of transmission

The prevalence of transmitted INSTI mutations remained low, although the number of patients on INSTI was increasing from 259 in 2008 to 2,180 in 2014 (Appendix 2). The low prevalence may be explained by the low number of patients who were potential transmitters of INSTI resistance. Between 2008 and 2014, 85 patients failed an ART including INSTIs in the entire SHCS database. Fifty-six of these 85 (61%) changed the treatment after a median of 49 days (IQR: 15-167) following treatment failure and a large proportion of these patients reached viral suppression (< 50 HIV-1 RNA copies/mL) later on (42 of 47 patients with a measurement, 89%).

GRTs were performed in 54 of 85 (64%) patients failing INSTI treatments. In 26 (48%) of these GRTs INSTI mutations were found. The following major mutations were most commonly detected: N155H (n=18, 33%), Q148H (n=4, 7%), Y143C (n=4, 7%) and Y143R (n=3, 6%). In addition, 13 GRTs with drug resistant viruses were performed from samples of patients who had detectable viral load on an ART containing INSTI but did not fulfill our criteria for treatment failure. However, the majority of patients ever detected with a major INSTI drug resistance mutation were successfully (HIV-1 RNA <50

copies/mL) treated at the last study visit (23 of 40, 58%), died (4 of 40, 10%) or stopped participating in the SHCS (8 of 40, 20%). Our findings reveal that only a very small number of patients are known to be potential transmitters of INSTI resistance mutations.

Comparison to the introduction of other drug classes

The transmission of drug resistance mutations against other drug classes was higher in the years following introduction [2]. An explanation for the difference is that the number of patients who failed on a treatment containing the other drug class was higher compared to the number of patients who failed on INSTI-treatments (Appendix 2). As mentioned above, in the first seven years after the introduction of INSTIs only 85 of 2,751 patients on INSTIs failed treatment. In the seven years after the introduction of unboosted PIs, PI/r and NNRTIs, 18.2 times (n=1,543 of 5,923), 5.7 times (n=482 of 5,332) and 7.2 times (n=609 of 4,347) more patients failed the respective ART. The median PVL after first exposure to INSTIs, after failure on INSTI and after detection of INSTI resistance in the seven years after introduction of the first INSTI was much lower compared to the median PVL after introduction of other drug classes (Figure 1, Appendix 3 and 4).

Discussion

Seven years after introduction of INSTIs in Switzerland, no transmission of major INSTI resistance mutations was detected by our study. The major reason for this unexpected absence of INSTI transmission is most likely the very low transmission potential in the SHCS. Treatment-naïve patients had no transmission potential of INSTI resistance because of lacking INSTI resistance mutations and the number of treatment-failures on INSTI remained remarkably low. Thus, the PVL of patients who experienced a virological failure on INSTIs or who carried viruses with INSTI drug resistance mutations was very low. To put these findings in a historical context was even more impressive. The transmission potential of resistance mutations remained very low after the introduction of INSTI compared to the time after introduction of PIs and NNRTIs.

Despite these very encouraging and unexpected findings, the transmission of INSTI resistance most likely cannot be avoided in the long run [6, 7]. Boyd et al. postulated that it is only a matter of time until the prevalence of transmitted drug resistance affecting INSTIs is reaching higher levels. However, we demonstrated that the transmission of drug resistance affecting a new class can be minimized. The Swiss setting cannot be compared to other settings, e.g. with limited access to viral load monitoring or no available second-line and third-line therapies. In these settings, patients may stay longer on failing regimens and may accumulate more drug resistance mutations. These patients have not only a high transmission potential. They might also accumulate secondary mutations. Such strains might be transmitted and fixed in the population and might lead to major public health issues in the future [2].

Minor mutations were more frequently seen in non-B subtype infections but they probably do not have an impact on the treatment outcome as it has also been shown for minor PI mutations [11, 12]. The sample size was too small to analyze specific pattern among non-B subtypes.

To our knowledge, this is the largest study assessing the transmission of INSTI drug resistance in a highly representative population. Due to the similar history of drug approval and treatment guidelines, our finding most likely also reflects the situation in other resource rich settings.

Our study is limited by the fact that not all patients with a failure on INSTI had a GRT performed. This was partially due to the fact that drugs were switched at low viral loads, making resistance testing less successful [13]. Viral load measurements and genotypic drug resistance testing is routinely integrated in clinical care in Switzerland since 1997 and 2002, respectively, therefore the PVL, number failures and mutations might be slightly underestimated. But this issue does not alter our conclusions.

To summarize, our study demonstrated that the transmission potential of drug resistance against a new drug class can be minimized in a setting coming very close to the World Health Organization target 90-90-90 [14, 15]. Nevertheless, it might only be a matter of time until the prevalence of

transmitted drug resistance affecting INSTI reaches notable levels. Of particular notice will be to investigate the effect of decreasing monitoring frequency that is proposed and performed in some countries. This may lead to delayed detection of treatment failures with subsequent emergence of resistance and a higher PVL of failing patients. From a global health perspective, it is important that the transmission potential in other settings can be minimized in a similar way.

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Conflict of interest

H. F. G. has been an adviser and/or consultant for GlaxoSmithKline, Abbott, Gilead, Novartis, Boehringer Ingelheim, Merck, Roche, Tibotec, Pfizer, and Bristol-Myers Squibb and has received unrestricted research and educational grants from Roche, Abbott, Bristol-Myers Squibb, Gilead, Astra-Zeneca, GlaxoSmithKline, and Merck Sharp and Dohme. E. B. has been consultant for BMS, Gilead, ViiV Healthcare, Pfizer, MSD, and Janssen; has received unrestricted research grants from Gilead, Abbott, Roche, and MSD; and has received travel grants from BMS, Boehringer Ingelheim, Gilead, MSD, and Janssen. S. Y. has been consultant for BMS and has received unrestricted research and educational grants from Roche, ViiV, and Gilead. T. K. served as an advisor for Bristol-Myers Squibb and Pfizer and has received travel grants from Abbott and Pfizer. M.B. has been an adviser and/or consultant for Gilead, Roche, Pfizer and has received unrestricted research and educational

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Figure legends

Figure 1: A-D) Population viral load (PVL) of patients treated with A) integrase strand transfer inhibitor (INSTI), B) non-nucleoside reverse transcriptase inhibitors (NNRTIs), C) unboostsed protease inhibitors (PIs) and D) ritonavir-boosted PI (PI/r) in the seven years after introduction of the drug class. The areas represent the PVL after first exposure to the specific drug class (light gray) and the PVL after virological failure on a specific drug class (dark gray).